# A MATCHED CASE-CONTROL STUDY ON PREDICTORS OF TREATMENT FAILURE IN PEOPLE LIVING WITH HIV/AIDS (PLWHA) ON ANTI-RETROVIRAL THERAPY IN A HIV CLINIC FROM SOUTH INDIA

**A Dissertation submitted in partial fulfilment of the degree**

**M.D (General Medicine) Examination of**

**The Tamil Nadu Dr. M.G.R. Medical University, Chennai**

**September 2010.**

# CERTIFICATE

This is to certify that the dissertation entitled *"A matched Case-control study on predictors of treatment failure in people living with HIV/AIDS (PLWHA) on Anti-Retroviral therapy in a HIV clinic from South India" is* the bonafide original work of Dr. Mucheli Sharavan Sadasiv towards the M.D. Branch-1 (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be conducted in 2010.

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# ABSTRACT:

**Background:** Since the time of NACO Antiretroviral (ART) role-out, generic ART has been the mainstay of therapy. There are many studies documenting the efficacy of generic ART but with the passage of time, treatment failure is on the rise. There are not many centres which provide free second line antiretroviral therapy. Through this study we aim to determine factors which contribute towards treatment failure in our cohort of patients.

**Methodology:** This was a matched case-control study assessing predictors for treatment failure in our cohort who had been on Anti-retroviral therapy for at least a year. We identified 42 patients (Cases) with documented treatment failure and 42 sex, age and duration of therapy-matched controls. Using a structured proforma, we collected information from the out-patient and in-patient charts of the ID clinic Cohort in CMC, Vellore. A set of predetermined variables were studied as potential risk factors for treatment failure on ART.

**Results:** Univariate analysis showed significant association with 1)Self-reported adherence<95%[OR 12.81(95%CI 1.54-281.45)], 2)Treatment interruptions in adherent cases[OR 9.56(95%CI 1.11-213.35)], 3)Past inappropriate therapies [OR 9.65(95%CI 1.12-215.94)], 4)Diarrhoea [OR 16.40(95%CI 2.02-355.96)], 5)GI opportunistic Infections [OR 11.06(95%CI 1.31-244.27)] and 6)Drug Toxicity [OR 3.69(95%CI 1.15-12.35)].

In multiple logistic regression analysis, we found independent risk factors of treatment failure to be: *Self-reported non-adherence (<95%) with OR 15.46(95%CI 1.55 – 154.08), drug toxicity – OR 4.13(95%CI 1.095 – 15.534) and history of diarrhoea – OR 23.446(95%CI 2.572 – 213.70).*

**Conclusion:** This study reveals that besides adherence to therapy, presence of diarrhoea and occurrence of drug toxicity are significant risk factors associated with failure of anti-retroviral therapy. There is a need for further prospective studies to elucidate their role in development of treatment failure on ART and thus help development of targeted interventions.

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# ABSTRACT

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A matched Case-control study on predictors of treatment failure in people living with HIV/AIDS (PLWHA) on Anti-Retroviral therapy in a HIV clinic from South India

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# INTRODUCTION

## Epidemiology of HIV/AIDS:

The growing epidemic of HIV infection continues to be a challenge to mankind. The prevalence of the HIV infection as predicted by the WHO 10 years back was only half the number as the current prevalence of the PLWHA. The number of people living with HIV worldwide continues to grow, estimated to have reached 33.4 million (31.1 million–35.8 million) by 2008. The number of people living with HIV infection in 2008 was more than 20% higher than the number in 2000, and the prevalence was roughly threefold higher than in 1990.

The prevalence is not uniform. There is a considerable geographical variation with the majority of the infection in the developing countries like Africa and India. The prevalence of HIV in India is 2 million to 3.1 million [1]. There is growing population of HIV affected people in India and along with other communicable diseases it poses a great threat to humanity [2].

## Trends in HIV prevalence:

The growing population of people with HIV infection reflects the combined effects of continued high rates of new HIV infections and the beneficial impact of antiretroviral therapy. As of December 2008, approximately 4 million people in low- and middle-income countries were receiving antiretroviral therapy—a 10-fold increase

over five years (World Health Organization, United Nations Children's Fund, UNAIDS, 2009). The latest epidemiological data indicate that globally the spread of HIV appears to have peaked in 1996, when 3.5 million [3.2 million–3.8 million] new HIV infections occurred. In 2008, the estimated number of new HIV infections was approximately 30% lower than the peak of the epidemic which occurred 12 years ago.

HIV-related mortality appears to have peaked in 2004, when 2.2 million [1.9 million–2.6 million] deaths occurred. The estimated number of AIDS related deaths in 2008 was roughly 10% lower than in 2004.

## Impact of Anti-retroviral therapy:

With the increase in the number of people living with HIV infection, there has been an increase in the understanding of the disease process and also the availability of the drugs in the treatment [3]. Previous decade has seen an evolution in the treatment of HIV infection from Monotherapy to Combination therapy in India [4]. The combination therapy has greatly reduced the viral load, improved the quality of life and decreases the resistance. In India, there are 226 ART centres which distribute free combination therapy. There are around 280,954 patients in India alive and taking free ART through the NACO ART centres [5]. Though the resources are limited, India has devised effective ways of distributing ART drugs [6].

## Problem statement – Anti-retroviral therapy failure :

The challenge that faces the ID physicians/physicians involved with the treatment of PLWHA with HAART is that of failure of virological and immunological response over the course of therapy. Different studies have quoted different rates of incidence of treatment failure and it differs with various factors. There is a need to address the problem of treatment failure and to look into the factors that predispose to the same.

## AIMS :

To study the profile of patients with treatment failure (virological or immunological or clinical) on generic Anti-retroviral therapy in the cohort of patients followed up at the ID clinic, CMC Vellore.

## OBJECTIVES :

1. To study the profile of individuals on generic ART.
2. To determine putative risk factors possibly contributing towards development of treatment failure in a cohort of individuals on generic ART.
3. To study the patterns of genotypic resistant mutations and correlating with clinical outcomes in patients with treatment failure on ART.

# LITERATURE REVIEW

## Stages and Natural history of HIV infection:

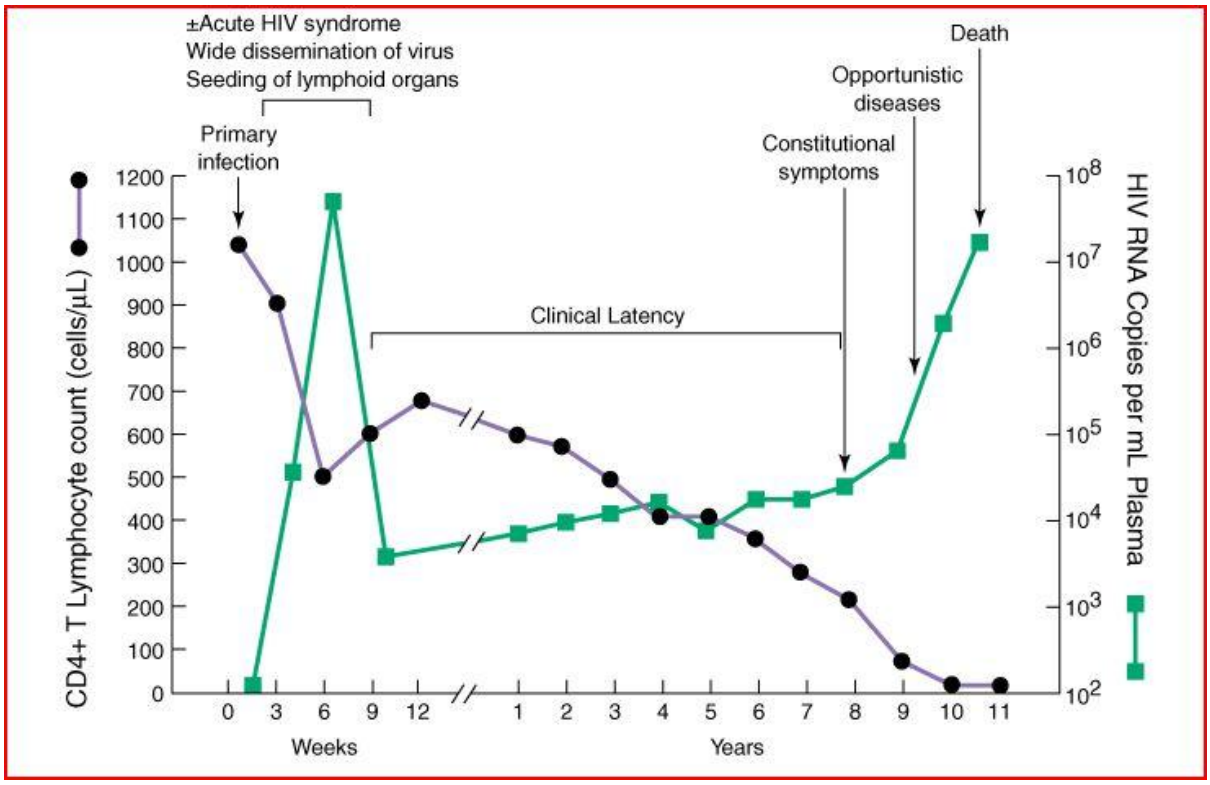
HIV-1 infection is divided into stages of primary infection with seroconversion, clinical latency, early symptomatic disease and AIDS. The mode of acquisition is mainly through heterosexual transmission in developing countries; and in countries such as the United States, men who have sex with men (MSM) also account for a sizeable number of HIV/AIDS diagnoses. Risk factors for transmission include high plasma HIV viral load and presence of ulcerative genital sexually transmitted diseases.

Symptomatic primary HIV infection occurs in many patients and has been reported in all major risk categories. The presence of symptoms and a prolonged illness correlates with more rapid progression to AIDS.

The period of early HIV disease extends from seroconversion to six months following HIV transmission. During the period of asymptomatic infection, patients generally have no findings on physical examination except for lymphadenopathy. Despite the lack of symptoms, high rates of HIV replication and CD4 T cell destruction may be occurring.

The stage of early symptomatic HIV infection is called "Class B" according to the CDC 1993 classification system and was formerly called "AIDS-related complex". The most substantive change in the classification system was the inclusion of all patients

with a CD4 cell count below 200/mm3 as having AIDS, regardless of the presence or absence of symptoms.




***<u>Graphical representation of Typical course of an untreated HIV-infected individual</u>***

***Adapted from www.uptodate.com***

## Pathophysiology of HIV infection:

HIV belongs to the lentivirus group of the retrovirus family. There are at least two types, HIV-1 and HIV-2. HIV-2 is almost entirely confined to West Africa although there is evidence of some spread to the Indian subcontinent. Retroviruses are characterized by the possession of the enzyme reverse transcriptase, which allows viral RNA to be transcribed into DNA, and thence incorporated into the host cell genome. Reverse transcription is an error-prone process with a significant rate of misincorporation of bases. This, combined with a high rate of viral turnover, leads to considerable genetic variation and a diversity of viral subtypes or clades.

On the basis of DNA sequencing, HIV-1 is divided into two subtypes:

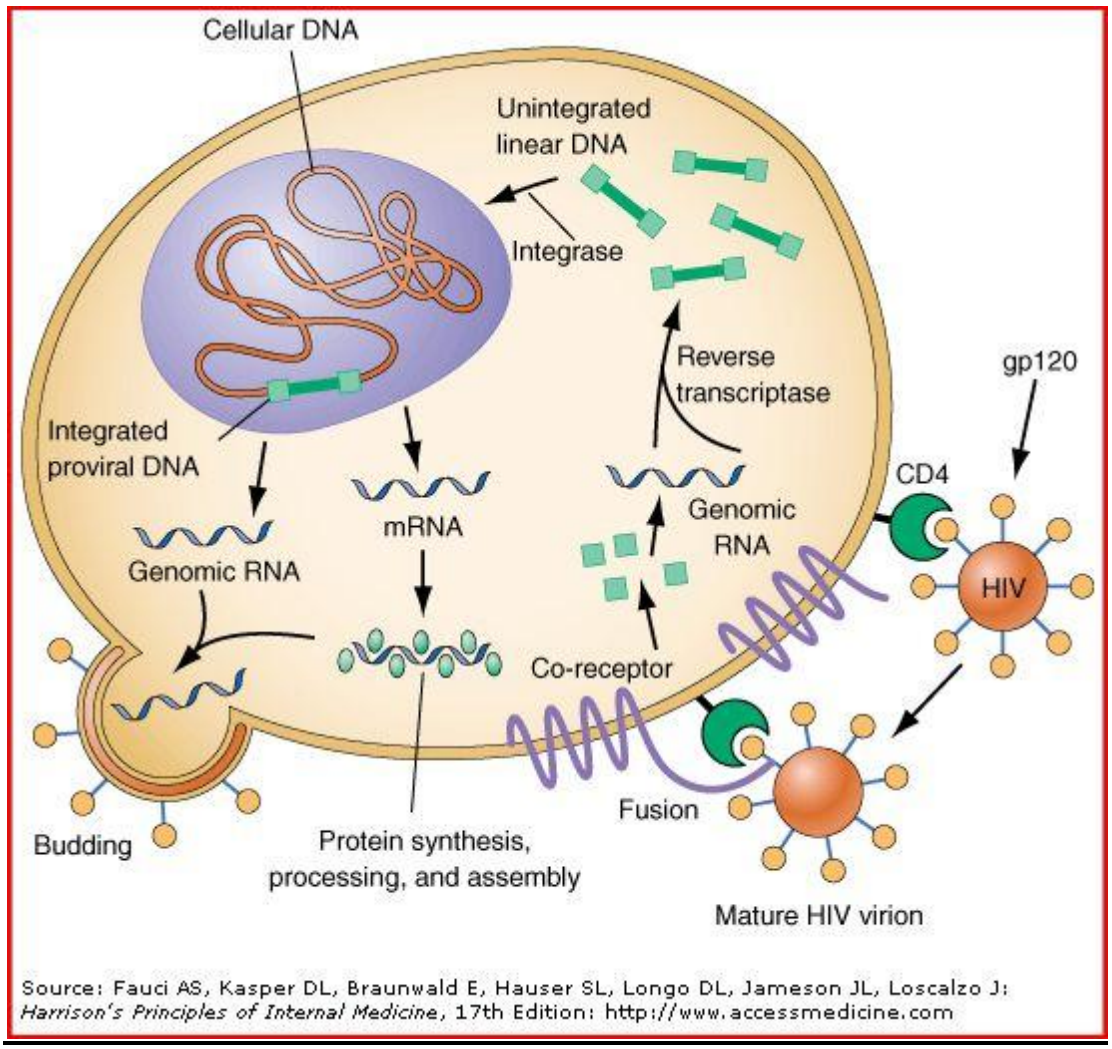
- *Group M (major) subtypes*. There are at least 10, which are denoted A-J. There is a predominance of subtype B in Europe, North America and Australia, but areas of central and sub-Saharan Africa have multiple M subtypes.
- *Group O (outlier) subtypes*. These are highly divergent from group M and are confined to small numbers centred on the Cameroons.

Recombination of viral material generates an array of circulating recombinant forms (CRFs), which increases the genetic diversity that may be encountered.

The interrelationship between HIV and the host immune system is the basis of the pathogenesis of HIV disease. The host cellular receptor that is recognized by HIV surface glycoprotein is the CD4 molecule, which defines the cell populations that are susceptible to infection. The interaction between CD4 and HIV surface glycoprotein together with chemokine co-receptors CCR5 and CXCR4 is responsible for HIV entry into cells.

Mutations in the gene expressing the receptor for chemokine CCR5 may impair entry of HIV into cells and therefore confer some resistance to this infection. Auxiliary viral proteins such as those coded by the *Nef* gene have a role in influencing host cell membrane proteins and signal transduction pathways. CD4 receptors and HIV surface glycoprotein interactions mediate the process of syncytium formation, which is a cytopathic effect of HIV infection.

Studies of viral turnover in HIV-infected individuals have demonstrated a virus half-life in the circulation of about 6 hours. To maintain observed levels of plasma viraemia, $10^8$-$10^9$ virus particles need to be released and cleared daily. Virus production by infected cells lasts for about 2 days and is probably limited by the death of the cell, owing to direct HIV effects, linking HIV replication to the process of CD4 destruction and depletion. Studies suggest that immunopathogenesis is a result of defective T cell homeostasis in HIV infection. The progressive and severe depletion of CD4 helper lymphocytes has profound repercussions for the functioning of the immune system. Cell-mediated immunodeficiency, which is the major consequence, leaves the host open to infections with intracellular pathogens, whilst the coexisting antibody abnormalities predispose to infections with capsulated bacteria. HIV also has a direct effect on certain tissues, notably the nervous system.




***<u>The replication cycle of HIV (depicted above)</u>***

Of note, is also the site of action of various anti-retroviral agents, viz.Fusion inhibitors, Reverse transcriptase inhibitors, Protease inhibitors, Integrase inhibitors etc,.

## Anti-retroviral therapy:

The currently available ARV drugs cannot eradicate the HIV infection from the human body. This is because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection and persists within the organs/cells and fluids (e.g., liver and lymphoid tissue) even with prolonged suppression of plasma viraemia to <50 copies/ml by antiretroviral therapy. The goal of therapy is essentially to reconstitute immune status both quantitatively and qualitatively and there by improve quality of life by preventing opportunistic infections as well as HIV-associated illnesses.

According to the NACO programme guidelines for treatment of HIV, all persons registered for care and treatment at ART centres should have their full history taken and undergo clinical examination, including determining the clinical stage of HIV. The initiation of ART is based on the clinical stage and the CD4 count is used to guide treatment and follow-up. The lack of a CD4 result should not delay the initiation of ART if the patient is clinically eligible according to the WHO clinical staging, but a CD4 test should be done as soon as possible.

It is recommended not to start ART in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART.

The following are the current NACO guidelines (2007) to start HAART in adults

- Offer ART to symptomatic patients if the CD4 count is 200–350 cells/mm3.
- Consider ART for asymptomatic patients with CD4 count between 200-350 cells/mm3 and monitor closely for new symptoms.
- If the CD4 count is 200–250 cells/mm3, physicians can consider repeating the CD4 test in 4 weeks in asymptomatic patients. This is to rule out the possibility of a 20% margin of error in laboratory results.
- Patients should start ART before the CD4 count drops below 200 cells/mm3.

Currently, the national programme provides the following combinations for first-line regimens

- Stavudine (30 mg) + Lamivudine (150 mg) + Nevirapine (200 mg) OR Efavirenz (600 mg)
- Zidovudine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg) OR Efavirenz (600 mg)

Principles for selecting the first-line regimen

1. Choose 3TC (lamivudine) in all regimens

2. Choose one NRTI to combine with 3TC (AZT or d4T)

3. Choose one NNRTI (NVP or EFV)

## Incidence of treatment failure on ART:

As the number of people with HIV/AIDS on anti-retroviral therapy is on the rise, the numbers with treatment failure will also rise. The resulting virologic failure diminishes the potential for long-term clinical success. This proves to be a major problem, at both individual level and as a public health concern. Drug-resistant strains of HIV selected through ongoing replication in the presence of ART also can be transmitted to uninfected or drug-naive patients, leaving them with fewer treatment options [7].

In Uganda, Weidle et al. have reported phenotypic drug resistance as high as 36% in patients in the highly active ART program [8]. Dragsted and others reported an incidence of treatment failure at 12 months in their study group as 11.6 per 100 person-years of follow-up [9]. The cumulative incidence of treatment failure in a cohort of 1370 adult patients in a study from the largest public HIV care centre in India was 3.9% (95% CI 2.9 to 4.9) [10].

Inspite of the variation in the percentage of treatment failure on ART(largely due to the population characteristics, lack of standardised definitions for treatment failure among various studies), it is pertinent to understand that the problem of treatment failure is real and growing. Also high cost, deficiency of reliable laboratory facilities, and inadequately trained personnel prohibit the assessment of treatment failure by viral load monitoring in resource-limited settings.

## Possible risk factors for treatment failure with ART:

Various risk factors for treatment failure with ART have been studied.

To list a few,

1. Poor adherence to medications/Missed visits
2. Prior virologic failure in previously treated patient
3. Higher baseline HIV RNA measurement (viral load)
4. Lower CD4 cell count at baseline
5. Younger age

However, there are several other factors that need consideration as they could have an implication in the development of resistance to ART such as

i) Pharmacokinetics

ii) Resistant strains of the virus in the population

### 1. *Poor adherence to Medication:*

Adherence to medications is probably the most important factor predicting ART success. This has been shown repeatedly in various studies. [11] [12] [13] [5] [14] [15]. Adherence to ART also plays an important role in viral load suppression and immunological reconstitution. Studies have established that Antiretroviral adherence is a strong predictor of progression to AIDS and [16]death, next only to CD4 count [17] [18] [16]. Even though adherence has been predicted as the important factor of long term virological suppression, it has been shown in various studies that adherence to ART is only 70%, in spite of the fact long term suppression requires near–perfect adherence. [13] [19-20].

Though adherence is consider as the important factor, the tools used for adherence and health care professional who uses these stools are still unskilled in assessing medication adherence [5, 13, 21]. Non-adherence to ART, likewise, is common in all groups of treated individuals. The average rate of adherence varies by the method used to assess it and the group studied, but appears to be approximately 70%. For example, in a prospective study, 140 individuals in a public hospital HIV clinic were followed for 1 year after initiation of ART. The investigators assessed adherence using 3 methods: a computer chip embedded in a specially designed pill-bottle cap to record the time and duration of each bottle opening (microelectronic monitoring system [MEMS], or MEMS caps), pill count, and self-report [20]. They calculated a composite adherence rate including all 3 measures that demonstrated a mean adherence rate of 71%. Only 6% of the patients took >=95% of their medications, the optimal level for durable virologic and clinical success.

Adherence measurements can be grouped into measures based on a patient's self-report of pill-taking behaviour and measures that are objective surrogates of pill-taking behaviour, such as pill count or MEMS caps. While it is difficult to compare studies using different measures of adherence, mean adherence was suboptimal in the following disparate groups of HIV-positive individuals: in a large multicenter clinical trial (85% adherence by self-report), [22] among patients from a veterans and university hospital (75% by MEMS), [13] among the marginally housed (89% by self-report, 73% by pill count, 67% by MEMS), [23] among those with serious mental illness (66% by MEMS), [24] among predominately minority women (64% by MEMS), [25] and among 2 different groups of inner-city residents with a history of injection drug use (80% by pill count, 53.5% by MEMS in one group, [26] and 78% by self-report, 53% by MEMS in the other group [27].

***Predictors of Adherence:***

A number of factors have been associated with non-adherence to ART. Understanding these factors can increase a clinician's attention to adherence when working with particularly susceptible patients and can inform the development of interventions to improve adherence.

Several excellent reviews addressing the predictors of adherence have been published [28] [29]. As described by Reiter and by Ickovics *et al* in separate publications, the factors associated with medication adherence are commonly divided into 5 intersecting categories [29].

1. Patient characteristics
2. Treatment Regimen
3. Disease Characteristics
4. Patient-Provider Relationship
5. Clinical Setting

Patient characteristics is broad terminology, which includes wide range of features from socio-demographic profile (like age, gender, economic status, educational status, etc) to psychological factors (knowledge about the disease and treatment, depression, attitude of the family members, pre-existing psychological morbidity present). There is paucity of data addressing each and every characteristic but there are few good reviews. [20] [13] [22] [14] [30] [12] [31] [32].

Though association between the socio-demographic profile and adherence is conflicting when the association is found between the few characteristics it is consistent. The following characteristics are repeatedly associated with the poor rate of adherence

i. Low socioeconomic status
ii. Low literary status
iii. Unstable housing
iv. Race/ethnicity

The factors that are surprisingly are not consistent are gender, educational status and insurance status. This can be explained because most of the studies were done in developed countries but in developing countries like India where there exists a strong bias towards gender & literacy, one would expect conflicting results from that described.

Psychological factors have profound influence on the adherence to medications. Though the disease itself can cause psychological manifestations this again adds to the pre-existing morbidity. The features more consistently found to associated are depression, pre-existing psychiatric disease, alcohol dependence or drug abuse and more stressful lifestyle.

Treatment in HIV infection has evolved from monotherapy to combination therapy over the last decade. There has been a uniform use of CD4 counts for the initiation of ART. The factors that could possibly influence the treatment characteristics included the number of pills prescribed, the complexity of the regimen, the specific type of antiretroviral drugs, and the short- and long-term medication side effects. Of the above mentioned features, only number of pill usage has been consistently associated with poor

adherence even when the other factors are fulfilled. The specific type of pill used did not show any significant association with adherence.

The disease characteristics include the stage of the HIV infection, duration of the infection, presence or absence of opportunistic infection and HIV related symptoms. Few studies describe poor adherence with a low CD4 cell count, and more adherence in the presence of opportunistic infection. Though the evidence is conflicting because most of the opportunistic infection are seen in patient with low CD4 cell counts, it can be postulated opportunistic infection adversely affect the patient daily activities where as CD4 count is the laboratory parameter. The duration of illness alone is difficult to study because of longer the duration of illness more the influence of other factors. The duration of illness didn't show any consistent association between adherences.

Patient-provider relationship is important for treatment for any chronic diseases. This factor has been extensively studied and documented in western literature whereas in our country these features are less studied and largely underestimated. Given the fact that a patient has the autonomy to choose what suits him/her the best for his/her condition, the characteristics that may affect adherence include the patient's overall satisfaction and trust in the provider and clinic staff, the patient's opinion of the provider's competence, the provider's willingness to include the patient in the decision-making processes, the affective tone of the relationship (warmth, openness, cooperation, etc), the concordance of race/ethnicity between patient and provider, and the adequacy of referrals.

In India there are around 226 ART centres which distribute free ART to 280,954 patients [5]. The prevalence of HIV infection is around 2.5 million. Though the exact data of the people living below CD4 cell count below 200 is not known it would be considerably higher. One reason for the lack of initiation and subsequently adherence is

the access to health care centre. Access to the ART centre has great impact on adherence to the medication. The characteristics of the clinical settings that influences adherence are access to ongoing primary care, involvement in a dedicated adherence program, availability of transportation and childcare, pleasantness of the clinical environment, convenience in scheduling appointments, perceived confidentiality, and satisfaction with past experiences in the health care system. The closer the ART centre, there is increased rate of adherence. Though we don't have any substantial evidence to show in treatment of HIV infection, this factor has been extensively studied in other chronic clinical conditions. [33].

*Measure of adherence:*

There are different techniques used in research methodology to measure adherence. But applying this in clinical setting is difficult. In resource poor setting this becomes quite challenging to the team of therapist. [20] [13] [34]. The following are some of the measure used to measure adherence

i. Pill count
ii. Medication Event Monitoring System (MEMS) cap
iii. Serological markers-plasma viral load, CD4 cell count
iv. Hospital visit data

Ensuring adherence is not the work of a single physician. rather it is team work consisting of physician, nurses, pharmacist, counsellors, and other health care individual. Accurately assessing adherence requires clinicians to develop a collaborative and nonjudgmental relationship with patients. The key to asking patients about their adherence is not in the specifics of the tool used but in taking the time to ask about adherence regularly, and doing so in an open and truly inquisitive manner. Otherwise,

many patients will simply state what they believe the clinician wants to hear: that they have been perfectly adherent.

In conclusion, improving adherence requires a combination of methods appropriate to the patient and clinical setting. Certain modifiable factors that influence adherence include depression, substance abuse, homelessness, and the therapeutic relationship between patient and provider should be addressed in a proactive and ongoing manner. Measures to improve adherence includes dedicated educational and collaborative time with every patient to plan for medication adherence and to maintain necessary support and collaboration throughout the course of treatment. This combined approach would address the entire spectrum of problems that varies commencing side effects dealt with, medications simplified or changed if necessary, and adherence devices supplied where appropriate. Adherence is the responsibility of the clinical team which occupies a higher rank in ART therapy. What is probably required, however, is a commitment to ask about and support medication adherence regularly in an open, nonjudgmental, and collaborative manner.

2. *Prior virological failure*

World health organization (WHO) defines treatment failure of either a decrease in CD4 count to the baseline or below, or a 50% decrease from the on-treatment peak value (if known), or CD4 concentrations persistently less than 100 cells/ml. [35]. Prior virological failure has more influence on the current treatment because of resistance of the virus, need of second line anti-retroviral agents for anticipated virological suppression, increase in adverse drug reaction, high cost, more hospital visits and poor adherence.

Research is needed to identify whether intensive patient education, with targeting of high-risk groups, can maximize the success of HAART in real-world practice. Future

studies of antiretroviral agents should address sex differences in pharmacodynamics and adverse drug reactions. [36] [37]. Poor viral load suppression is associated with higher rate of opportunistic infection.

### 3. *Higher baseline HIV RNA measurement*

High baseline HIV RNA has been shown be one of the predictors of treatment failure. But the association is not strong. In some, there is poor or no correlation with the high viral RNA load and treatment failure. Though it is theoretical for one to assume this it is not true because patient with high viral RNA load are more often symptomatic and have good adherence to treatment. In trials involving those patients there tend to be more bias because of the close follows up of these patients as compared to those with low viral RNA load.

High viral load indirectly indicates virulence of the virus to overcome the host immune system, chronicity of the infection, and poor host immune defence mechanism. The immune system of the host is destroyed thoroughly predisposing the host to the opportunistic infection which increase the mortality and morbidity associated with HIV infection. The high viral RNA load is associated with treatment failure though the association is not too strong it will be wise to start ART and suppress the viral RNA load because the longer the duration of the patient with increase in viral RNA more the complication rate. [38]

### 4. *Lower CD4 cell count*

Low CD4 cell count is associated with treatment failure and development of resistance. In a study done by Deek *et al,* they showed the there is an increase in the resistance when protease inhibitor is used with low CD4 cell count. There aren't any

subsequent studies showing the relationship of combination therapy and low CD4 cell count in treatment failure. However the combined data from different studies predicted that low CD4 cell count is associated with treatment failure. The reason for this is multiple like increased risk of opportunistic infection, increased chance of immune reconstitution inflammatory syndrome, development of resistance to the baseline anti-retroviral agent and generally theses patient are malnourished. [38]

### 5. *Other factors*

There are a number of other factors that influence the treatment outcome in ART. But these factors have not consistently or measurably shown to be predictors of treatment outcome. The factors associated are older age, poor socioeconomic status (independently), other chronic medical condition, educational qualifications, occupation, social status etc,. These factors both independently and also together influence the treatment. It is difficult to study each of these factors independently but studies show that these factors individually affect the treatment outcome.

## *Antiretroviral therapy absorption:*

### ***Pharmacokinetic implications***

The use of multidrug antiretroviral therapy for HIV-infected patients, and the need for these patients to receive multiple concomitant drugs for either the treatment of opportunistic infections or the management of drug-related adverse events, makes it imperative to understand the pharmacokinetics of all the drugs in the regimen as well as the possible implications on development of resistance. Inter-patient variability in drug absorption, distribution, metabolism and excretion can all contribute to variability in plasma drug concentrations.[39].

Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are primarily metabolised by the cytochrome P450 (CYP450) enzyme family. Any drug that acts as an inhibitor or inducer of the CYP450 system can cause significant change in plasma drug concentrations.[40]

### ***Anti-retroviral drug malabsorption:***

#### ***Diarrhea and resistance***

A study from Brazil found that one or more antiretroviral drugs are malabsorbed in virtually all patients with diarrhoea and wasting, assessed in this setting by plasma levels of the drugs. Furthermore genotypic testing revealed that viral resistance to the drugs being malabsorbed is often associated [41]. This study also demonstrated that addition of alanyl-glutamine and glutamine in treating diarrhoea may help to improve

therapy for patients with AIDS who have diarrhoea and/or wasting in developing, tropical areas.

***Role of Therapeutic drug monitoring***

The introduction of TDM represents a major step in the way to optimize antiretroviral therapy for each individual. Firstly, it can improve the response to treatment by just modifying drug doses. There is no doubt that the integrated use of TDM and drug resistance testing will result in a significant improvement in the management of antiretroviral therapy.

Secondly, an important application of TDM concerns the adherence issue. This aim should be used cautiously because serum concentrations may reflect drugs administered within the past 24 hours but say nothing about medications taken days or weeks before blood sample collection.

Monitoring hair levels has been proposed as a good method to assess past adherence based on the continued growth of the hair and the accumulation

of the drug in this tissue.

Thirdly, TDM also seems to be of great utility to detect drug-drug and drug-food interactions and malabsorption problems, and could allow dose adjustment in order to maintain effective plasma concentrations.

However, more studies are necessary to determine a therapeutic range in which plasma drug concentrations need to be kept. The recognition of toxic and suboptimal drug concentrations needs to be established for each compound. Controlled-concentration therapy seems to be the most appropriate strategy to maintain serum drug concentrations

much higher than the IC95 for each drug. There is a need for a reliable estimation of the IC90 for *wild type* as well as mutant HIV strains.

Fourthly, PIs and NNRTIs are the most appropriate candidates for TDM. The applicability is still unclear for NRTIs, since they need to be intracellularly phosphorilated to become active.

Finally, the additional costs of TDM as part of clinical routine exams need to be balanced against an expected reduction in pharmaceutical costs. Dose individualization needs to be pursued in each individual for providing an effective drug concentration. This represents a more rational use of antiretroviral drugs and might prevent therapeutic failure due to low plasma drug concentrations.[42]

## ***Drug resistance***

Resistance to ARVs results from mutations in the protease and reverse transcriptase genes of the virus. HIV has a rapid turnover with $10^8$ replications occurring per day. The error rate is high, resulting in genetic diversity within the population of virus in an individual. This mixture will include drug-resistant mutants. When drugs only partially inhibit virus replication there will be a selection pressure for the emergence of drug-resistant strains. The rate at which resistance develops depends on the frequency of pre-existing variants and the number of mutations required. Resistance to zidovudine occurs with an accumulation of mutations, whilst a single-point mutation will confer high-level resistance to all three NNRTIs.

HIV antiretroviral drug resistance testing has become routine clinical management of the HIV patient. Genotypic assays to determine the genetic structure of the RT and protease genes of HIV are available. The tests are based on PCR amplification of virus and give an indirect measure of drug susceptibility in the predominant variants. Such assays are limited both by the starting concentration of virus, most assays requiring at least 1000 copies/mL of blood, and by their poor ability to detect minority strains. For results to be useful, samples must be analysed when the patient is on therapy, as once the selection pressure of therapy is withdrawn, wild type virus becomes the predominant strain and resistance mutations present earlier may no longer be detectable.

The use of genotypic assays with appropriate interpretation in patients for whom therapy

is failing has shown significant virological benefits. Phenotypic assays provide a more direct measure of susceptibility but the complexity of the assays limits availability and no additional advantage has been demonstrated. In the UK, increasing numbers of patients are infected with viral strains originating in sub-Saharan Africa, which may require modification of the assay and the interpretation of the results.

There is evidence for the transmission of HIV strains that are resistant to all or some classes of drugs. Studies of primary HIV infection have shown prevalence rates between 2-20%. Prevalence of primary mutations associated with drug resistance in chronically infected patients not on treatment ranges from 3% to 10% in various studies.

# MATERIALS AND METHODS

## Study design

The study is a matched case-control study from the cohort of patients attending HIV/ID clinic in Christian Medical College, Vellore during the period *January 2000* to *August 2009*.

CMC Vellore is a 2200 bedded tertiary care, multispecialty teaching hospital in Southern India. It caters to patients from all over India. The first case of HIV infection in India was diagnosed here in the Department of Clinical Virology in 1986 and since then, the Department of Medicine-I and Infectious Diseases has been actively involved in HIV clinical care and treatment. At present the Infectious Diseases department has been taking care of all the complex HIV and infectious diseases related problems. Every PLWHA after being started on ART, is transferred to our Infectious Disease (ID) clinic which exclusively caters to HIV patients though they are also seen in our routine infectious disease referral clinics as well.

The ID clinic is an interdisciplinary clinic run by the departments of Medicine, Paediatrics, Obstetrics and Gynaecology, Dermatology and STD and Psychiatry. It also includes 3 well trained and experienced counsellors and pharmacists. The annual out-patient load of our ID clinic is around 3000 patients, apart from the cases seen in our NACO ART centre and referral clinics. The Clinical Virology Department at CMC Vellore is a national reference laboratory centre for HIV testing. The hospital has a well-developed system for infection control and exposure prevention and has instituted a

comprehensive HIV policy also providing post exposure prophylaxis to all its employees. From January 2000 till the end of August 2009, a total of 823 patients were on antiretroviral therapy and constituted the ID clinic cohort on follow-up. Of these, 116 patients were on self-paid ART, while the rest i.e. 707 patients were initiated on free NACO ART. 178 patients on NACO ART were transferred out to other ART centres for closer follow-up (Tamil Nadu as well as other states in India).

The generic ART comprised of a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). The NRTIs included Stavudine, Zidovudine and Lamvudine and the NNRTIs used were Nevirapine and Efavirenz.

## Case definition

We defined cases as adults (age > 16 years) with documented treatment failure (defined as either clinical/immunological or virological failure as per criteria by WHO[43],[35]) from the above-mentioned cohort, who had been on ART for a minimum duration of 12 months.

*We also defined treatment failure as follows*

*Clinical failure - New or recurrent WHO stage 4 condition*

*CD4 cell/Immunological failure defined as*

- *Fall of CD4 count to pre-therapy baseline (or below); or*
- *50% fall from the on-treatment peak value (if known); or*
- *persistent CD4 levels below 100 cells/mm3*

*Virological failure - Plasma viral load above 5,000copies/ml*

## Control selection

Controls were age (+/- 5 years) & sex matched PLWHA on regular follow-up with us who were on ART for a similar duration (+/- 6months) as the cases. Controls were selected in a non-random fashion from the cohort. Random selection was deemed unnecessary as it was a matched case-control study. We matched controls for possible confounders like duration of therapy, age and sex.

## Data collection

Demographic and treatment details were noted on data information sheets using the data available from the Out-patient/In-patient records maintained by the Medical records department.

## Sample size

Sample size was calculated based on a proportion of patients found to have treatment failure from a study done in Mumbai

*A cross-sectional study among HIV-infected patients who were receiving ART in 3 private outpatient clinics in Mumbai from December 2004 through April 2005 had found that 22% of patient with suppressed virological load to be non-adherent, with an adjusted odd's ratio 5.70 for an association with adherence>95% and virological suppression.[44]*

Using this data, sample size was calculated using Epi-Info ver6 statscal and we found that a sample size of 42 in each group would have 95% power with alpha-error of 0.05.

## Statistical analysis

SPSS ver.13 was the software used for data entry and statistical analysis.

For normally distributed continuous variables, independent two sample t-test was used to compare the means between the two study groups. Chi-square test or fisher's exact test was used to compare the categorical variables between the groups, as appropriate.

To identify risk factors independently associated with treatment failure, variables found to be significantly different between cases and controls in the univariate analysis were entered into a logistic-regression model. A value of $p<0.05$ constituted a significant difference. Odds ratios and 95% CI were obtained.

# RESULTS

From January 2000 to August 2009, a total of 823 patients were on antiretroviral therapy and being followed up in our ID clinic. Of these,116 patients were on self-paid ART, while the rest i.e. 707 patients were on NACO ART. 178 patients on NACO ART had been transferred out to other ART centres(Tamil Nadu as well as other states). 66 patients were identified as potential cases after carefully examining the case registry maintained in the pharmacy for anti-retroviral drugs, which works in conjunction with the ID clinic in CMC, Vellore. However, 24 patients could not be enrolled in the study for data collection and analysis because of various reasons (incomplete data entry/charts disposed off/ no appropriate controls/Children).

## ***Baseline characteristics***

42 cases were considered appropriate for inclusion in the study and 42 controls were selected and matched for age, sex and duration of therapy.

As defined by the WHO criteria for treatment failure, majority 33/42 (78.6%) had documented virological failure; and in those who couldn't afford quantitative viral load, CD4 counts documented immunological failure. A significant number of cases were detected early based only on virological failure 13/42(30.9%).There was evidence of clinical failure in 20/42(47.6%) of the total cases studied.

Genetic susceptibility testing was performed in 21 out of the 33 cases who could afford viral loads. We found high-level resistance to NNRTIs (NVP/EFV) and 3TC/FTC in all of them (100%) whereas only 7 cases had high-level resistance to AZT/d4T or

Thymidine Associated Mutations (TAMS). Only two out of the 21 had triple mutations – mutations to NNRTIs/NRTIs and PIs.

Majority of the cases were from outside Tamil Nadu 22/42 (52.4%) from Neighbouring states and 3/42 (7.1%) from the rest of India as compared to 10/42(23.8%) of controls. Most controls were from Tamil Nadu 32/42(76.2%) and in particular from in and around Vellore. The reason for this diverse geographic distribution was that most cases of treatment failure were referred patients to the CMC ID clinic for expert management whereas the controls were patients who had been enrolled under the NACO-ART programme and so tended to be locals. We did not match for geographic location as most of the patients seen in our ID clinic were referred to their closest ART centre.

All cases and controls were diagnosed to be HIV infected according to guidelines provided by the NACO algorithms for diagnosis of HIV infection.

None of the cases or controls in the study population were co-infected with Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV). None tested were VDRL positive.

The risk factor for acquisition of HIV among the cases was predominantly heterosexual intercourse. Among the controls again the predominant route was heterosexual intercourse but homosexual contact and blood transfusion contributed to one each.

Information on spouse testing for HIV was not available in majority of the cases.

Among the controls (on whom the data was available i.e. 50%) 2/3$^{rd}$ of the spouses were negative for HIV infection i.e. were discordant couples.

***WHO clinical stage prior to treatment:***

WHO clinical staging prior to therapy was also studied.

Nine (21.4%) cases as compared to 3(7.2%) controls belonged to Clinical Stages 1 and 2. Thirty three (78.6%) cases as compared to 39(92.9%) controls belonged to Clinical Stages 3 and 4. There was no statistically significant difference between the two groups.

***Pre-ART Opportunistic Infections (Pre-ART OIs) :***

Twenty-seven (64.3%) of cases had a documented opportunistic infections prior to the initiation of ART, as compared to twenty-five (59.5%) of controls, which was not statistically significant. Of these, eight each of the cases and controls with documented opportunistic infections had multiple OIs. There was no statistically significant difference between the two groups with regard to the incidence of various OIs.

Between the two groups,18 Cases were found to have Mycobacterial OIs compared to 15 in controls. Mycobacterial infections were the commonest OIs among this study population. 10 Cases were documented to have Candidial OIs compared to 14 controls. 2 cases and 2 controls were found to have Pneumocystis carinii pneumonia. 2 cases had CMV infections, while no control patient was documented to have CMV infection. One control was found to have cryptococcal OI, when no case was found to have cryptococcal infection. 2 Cases were diagnosed with Cryptosporidial diarrhoea prior to ART compared to 1 control.

***Table no. 1***

**Pre-ART opportunistic infections compared in both the group**

| Opportunistic infection | Cases | Controls | p-value |
|---|---|---|---|
| Pre-ART OIs | | | |
| *YES* | 27(64.3%) | 25(59.5%) | 0.65 |
| Multiple OIs (>1) | | | |
| *YES* | 8(19.1%) | 8(19.1%) | 1.00 |
| Type of Infection | | | |
| • *Mycobacterial* | 18(42.9%) | 15(35.7%) | 0.50 |
| • *Candidial* | 10(23.8%) | 14(33.3%) | 0.33 |
| • *Pneumocystis carinii* | 2(4.8%) | 2(4.8%) | 1.00 |
| • *CMV infection* | 2(4.8%) | 0 | 0.15 |
| • *Cryptosporidial infection* | 2(4.8%) | 1(2.4%) | 0.55 |

**LABORATORY PARAMETERS**

Various baseline laboratory parameters were compared between the two study populations and there was no statistically significant difference. [Ref Table 2]

***Table 2***

***Baseline characteristics of Study Population***

| Parameter | Cases n-42 | Controls n-42 | p-Value |
|---|---|---|---|
| *Matching Criteria* | | | |
| Age, mean in yrs(S.D.) | 43.5(+/-7.7) | 42.3(+/-6.9) | |
| Sex, M/F | 31/11 | 31/11 | |
| Duration of therapy(in months) | 38.8(+/-24.9) | 39.1(+/-22.7) | |
| *Baseline Characteristics* | | | |
| WHO Clinical Staging | | | 0.06 |
| *Stages 1 & 2* | 9(21.4%) | 3(7.2%) | |
| *Stages 3 & 4* | 33(78.6%) | 39(92.9%) | |
| Pre-ART OIs | | | |
| *Documented Pre-ART OIs* | 18(64.3%) | 19(59.5%) | 0.82 |
| *Multiple Pre-ART OIs* | 9(33.3%) | 6(24%) | 0.39 |
| Laboratory Parameters | | | |
| *Hemoglobin (g/dl)* | 11.15(+/-2.49) | 11.68(+/-2.05) | 0.288 |
| *Total WBC count(per cu.mm)* | 6190.48(+/-3085.27) | 6483.33(+/-3083.31) | 0.665 |
| *ALC(per cu.mm)* | 1557.0(+/-1052.31) | 1588.14(+/-860.41) | 0.882 |
| *AEC(per cu.mm)* | 285.76(+/-44.09) | 430.95(+/-66.49) | 0.434 |
| *Total serum protein (g/dl)* | 8.264(+/-1.03) | 8.300(+/-1.00) | 0.873 |
| *Serum Albumin (g/dl)* | 3.714(+/-0.70) | 3.581(+/-0.74) | 0.399 |
| *SGOT (IU/L)* | 48.40(+/-41.89) | 45.55(+/-54.80) | 0.789 |
| *SGPT (IU/L)* | 47.69(+/-50.08) | 36.48(+/-32.74) | 0.228 |
| *Baseline CD4 count*(cells/cu.mm)* | 122.17(+/-138.91) | 125.32(+/-75.64) | 0.901 |

**missing data – Cases(n=35), Controls(n=41)*
*ALC – Absolute lymphocyte count, AEC – Absolute eosinophil count*

***Genotypic drug resistance testing:***

Genotypic drug resistance testing was available on 21 cases (50%).

All of the twenty-one patients were found to have High-level resistance to NNRTIs. The most common mutations were Y181C, K103N, V106M, V108I and L234I.

Seven out of the 21 had high-level resistance to NRTIs, while all the 21 had significant mutations conferring resistance to Lamivudine/Emtricitabine. The most common mutations were M184V, D67N, K70E, V75M and M41L.

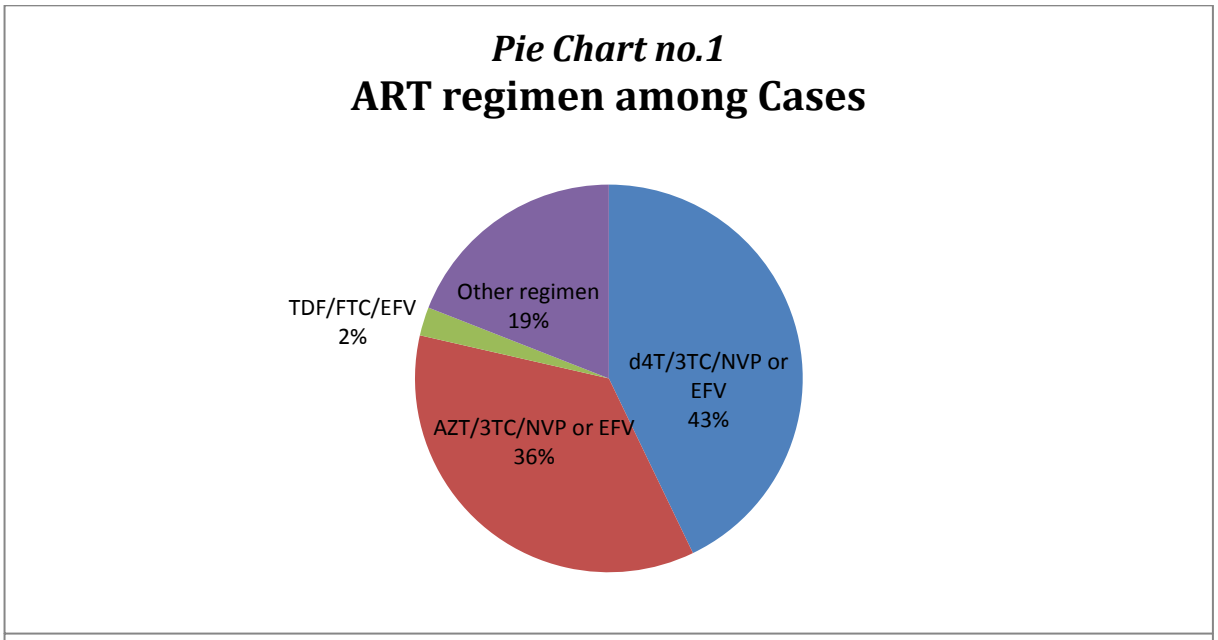
Only two of these patients had mutations to Protease inhibitors, and both were resistant to NNRTIs and NRTIs.

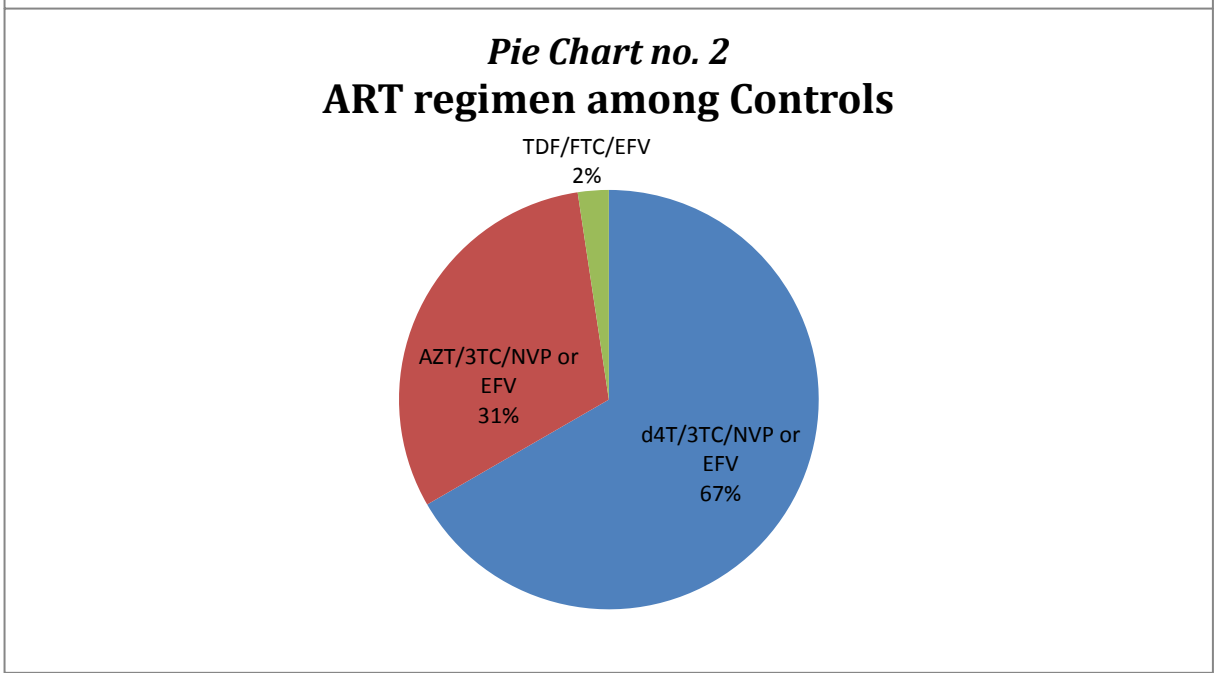
***Type of ART regimen & ART centre for Initial drugs:***

Type of ART regimen was different in both the study groups. 18 cases (42.9%) were started on a combination of d4T/3TC/NVP or EFV, as compared to 28 controls (66.7%). 15 cases (35.7%) had AZT/3TC/NVP or EFV as the initial regimen, as compared to 13 controls (31.0%). One case and a control each were on TDF/FTC/EFV regimen. 8 cases were started on other regimens, mainly dual therapy. No case or control had PI-based regimen as the initial choice of ART.

30 cases (71.4%) were paying for their ART medications as compared to 3(7.14%) controls. Since the NACO ART centre at CMC Vellore was started in April 2008, this reflects a probable selection bias as most of the controls selected were being followed up here.

***Pie chart 1(ART regimen in Cases) & 2(ART regimen in Controls)***



## *Risk factors* : ***UNIVARIATE ANALYSIS***

A series of putative factors were analysed. Odd's ratios were calculated with measures of significance (p-values).

### A. NON-COMPLIANCE

*Non compliance to therapy was divided into two specific categories*

*(a) Non- adherence*

*(b) Unstructured treatment interruptions*

### *NON-ADHERENCE*

Adherence was reported by patients themselves. Patients were asked about the number of pills missed and their *pill-diary* was examined to calculate the proportion of pills taken. All cases and controls had self-reported adherence of more than 80%. Adherence less than 95% was reported in 10 cases (23.8%) and one control (2.4%).

Odds ratio for non-adherence (<95%) associated with treatment failure was 12.81(95%CI 1.54 – 281.45) with a p-Value of 0.004, suggesting statistical significance.

***Table no. 3***

Adherence among cases & controls

| Self-reported Adherence | | | |
|---|---|---|---|
| | Cases | Controls | Total |
| >95% | 32 | 41 | 73 |
| % within Case/Ctrl | 76.2% | 97.6% | 86.9% |
| 80-95% | 10 | 1 | 11 |
| % within Case/Ctrl | 23.8% | 2.4% | 13.1% |
| Total Count | 42 | 42 | 84 |
| % within Case/Ctrl | 100.0% | 100.0% | 100.0% |

***UNSTRUCTURED TREATMENT INTERRUPTIONS***

Interruptions in treatment schedules (as brief as 10days), in otherwise adherent patients was also associated with treatment failure. These treatment interruptions were largely unstructured. It was either physician advised (in view of serious drug toxicity) or self-imposed by patient (various social reasons – intercurrent illness/fasting/inability to procure medications etc.). Seven cases (16.66%) had treatment interruptions due to any of the above reasons on a background of usual good self-reported adherence. Interrupted treatment was analysed as a risk factor for treatment failure and odds ratios calculated were found to be statistically significant i.e. 9.56(95%CI 1.11 to 213.35), p-Value of 0.0137 .

When **treatment interruptions** were combined with **non adherence,** OR 27.88(95% CI 3.50 to 596.37) with p-Value of 0.00002 was significantly associated with treatment failure.

***Table 4***

**Interrupted Treatment excluding poor adherence**

| | Case1/Ctrl2 | | |
|---|---|---|---|
| | 1 | 2 | Total |
| YES | 7 | 0 | 7 |
| % within Case1/Ctrl2 | 16.7% | 0.0% | 8.33% |
| NO | 35 | 42 | 77 |
| % within Case1/Ctrl2 | 83.3% | 100% | 91.6% |
| Total Count | 42 | 42 | 84 |
| % within Case1/Ctrl2 | 100.0% | 100.0% | 100.0% |

***B. Past inappropriate therapies (PIT)***

Improper regimens (e.g., dual regimens) and inadequate drug dosing were both identified as *Past inappropriate* therapies. Use of dual therapy in the past was identified as a potential risk factor for failure in 7(16.7%)of the 42 cases, 1(2.4% ) out of the 42 controls. One of the cases was also noted to have received sub-optimal doses of anti-retroviral therapy in the past. *PIT* was significantly associated with treatment failure. [OR 9.65 (95%CI 1.12 to 215.94), p-Value of 0.0135].

***C. Diarrhoea***

Presence of prolonged diarrhoea was defined as increased stool frequency or a change in stool consistency to a liquid state either continuously or in episodes). Twelve cases (28.6%) had a history of prolonged diarrhoea (more than one month) after the diagnosis of HIV infection, compared to one control (2.4%). This association was statistically significant. [OR 16.40(95%CI 2.02 – 355.96) p-Value of 0.0009]

***D. GI opportunistic infections – prior to and after initiation of ART:***

Eight Cases (19.4%) had documented GI opportunistic infections compared to none among the controls. Documentation of a GI opportunistic infection both prior to and after initiation of ART was significantly associated with treatment failure.[OR 11.06(95%CI 1.31 – 244.27) ; p-Value = 0.007]

***E. Medical Co-morbidities:***

Several medical co-morbidities including diabetes, hypertension, dyslipidemia, renal failure, alcoholism and other diseases such as Ischemic heart disease, Seizure disorder, Chronic Obstructive Pulmonary Disease etc. were compared between the two groups.

Presence of medical co-morbidity (p= 0.53) or any particular co-morbidity were not significantly associated with treatment failure (refer Table no.5)

***Table no 5.***

***Comorbidities between the two groups***

| Parameter studied | Odd's ratio(95%CI) | p-Value |
|---|---|---|
| Diabetes mellitus | 0.37(0.05 – 2.36) | 1.40 |
| Hypertension | 0.38(0.07 – 1.84) | 1.79 |
| Dyslipidemia | 3.33(0.55 – 25.68) | 0.13 |
| Alcoholism | 1.00(0.0 – 38.11) | 1.00 |
| Renal failure | 2.05(0.14 – 59.43) | 0.55 |
| Other medical co-morbidities | 3.00(0.92 – 10.15) | 0.04 |

***F. Use of other medications that could have possible interactions:***

Information on other medications that patients have been on, were looked at for potential interactions with anti-retroviral therapy leading to possible sub therapeutic levels of the antiretrovirals. The following drugs with likely drug-interactions were identified:

Antiepileptics (Phenytoin/Phenobarbitone/Valproate/Gabapentin),

Anti-diabetic drugs(Glipizide/Metformin), Statins/Fibrates,

Anti-hypertensives ( Amlodipine/Hydrochlorthiazide),

Anti-depressants (Amitryptilline/Sertraline),

GI drugs( Pantoprazole/Domperidone).

Drug interactions between ART and other drugs were not associated with treatment failure. [OR 1.15 (95%CI 0.37 - 3.59),p-Value 0.79]

***G. Drug toxicity:***

Drug toxicity or an adverse drug reaction to antiretrovirals or other drugs used in treatment of HIV infection were also studied for a possible impact on treatment failure with ART as they often require a modification of the ART regimen. 16 (38.1%) cases had experienced ADR as compared to 6 controls (14.3%).

***Table no 6***

***Adverse Drug reactions (ADR) compared between both the groups***

| Adverse Drug Reaction | Cases | Controls | p-value |
|---|---|---|---|
| Presence of Drug Toxicity | | | |
| *YES* | 16(38.1%) | 6(14.3%) | 0.013 |
| Multiple ADR (>1) | | | |
| *YES* | 4(9.5%) | 0 | 0.04 |
| Type of Drug Toxicity | | | |
| • *Skin Rash* | 6(14.3%) | 0 | 0.011 |
| • *Anemia* | 4(9.5%) | 1(2.4%) | 0.16 |
| • *Neuropathy* | 2(4.8%) | 1(2.4%) | 0.55 |
| • *Lipodystrophy* | 6(14.3%) | 1(2.4%) | 0.046 |
| • *Metabolic (Diabetes/Dyslipidemia)* | 2(4.8%) | 3(7.14%) | 0.64 |

Six (14.3%) cases developed drug rash, either to NVP or cotrimoxazole as compared to none among the controls. Six (14.3%) cases also had lipodystrophy as compared to one among the controls (2.4%). Four (9.4%) cases developed anaemia as compared to one among the controls. Two (4.7%) cases reported neuropathy compared to one control (2.4%). There were metabolic complications (diabetes/dyslipidemia) in 2 (4.7%) cases and 3 controls (7.14%). Four cases had more than one ADR compared to none in the controls.

Overall, drug toxicity was significantly associated with treatment failure.

[OR 3.69(95%CI 1.15 to 12.35); p-Value = 0.013].

We did not find severe drug toxicities like lactic acidosis, hepatitis and pancreatitis in our study population, which usually require stoppage or modification of the ART regimen.

Serious drug toxicities(in our study – Skin Rash) were found to be significantly associated with treatment failure however the CI was very wide. [OR 8.14 (95% CI 0.93 to 184.15) ; p-Value = 0.028].

***H. Occurrence of Immune reconstitution syndrome (IRIS):***

Four cases and 3 controls were documented to have IRIS after initiation of ART. Occurrence of IRIS had no significant association with treatment failure. IRIS documented among the cases were tuberculosis in 2, cryptococcal meningitis and disseminated MAC infection in one each.

Granulomatous prostatitis, Genito-urinary TB and Tuberculous meningitis were the diseases presenting as IRIS among the controls.

Univariate analysis identified the following variables to be significantly associated with treatment failure.

- Non-adherence
- Treatment interruptions in compliant patients
- Past inappropriate therapy
- GI opportunistic infections
- Diarrhoea
- Drug toxicity

***Table 7***

**Summary of Risk factors on Univariate analysis**

| Risk Factor | Odd's ratio(95%CI) | p-Value |
|---|---|---|
| Non-adherence (Self-reported adherence<95%) | 12.81(1.54 – 281.45) | 0.004 |
| Treatment Interruptions, *Excluding non-adherence* | 9.56(1.11 - 213.35) | 0.014 |
| Past inappropriate therapies | 9.65(1.12- 215.94) | 0.014 |
| Diarrhea | 16.40(2.02 – 355.96) | 0.0009 |
| Gastro-intestinal OIs | 11.06(1.31 – 244.27) | 0.007 |
| Use of drugs with possible interactions | 1.15 (0.37 - 3.59) | 0.79 |
| Drug toxicity | 3.69(1.15 - 12.35) | 0.013 |

## ***MULTIVARIATE ANALYSIS*** - LOGISTIC REGRESSION

The above variables were subjected to a Multivariate analysis, which incorporated these variables in a step-wise logistic-regression model. Non-adherence, drug toxicity and diarrhoea were identified as significant risk factors for treatment failure.

***Table 8***

**Summary of Risk factors on Multivariate analysis**

**(Logistic regression model)**

| Risk Factor | Odd's ratio(95%CI) | p-Value |
|---|---|---|
| Non-adherence (Self-reported adherence<95%) | *15.46 (1.55 – 154.08)* | 0.02 |
| Documented drug toxicity | *4.13 (1.095 – 15.534)* | 0.036 |
| Diarrhea | *23.446 (2.572 – 213.70)* | 0.005 |

# DISCUSSION

The purpose of this case-control study was to evaluate the potential risk factors that could predict treatment failure. By identifying the population at risk for treatment failure, targeted disease management interventions can be undertaken to improve outcomes of ART.

A study published from Treat Asia HIV Observational Database(TAHOD) reported 45 patients out of 1846 i.e. 2.43% stopping their first regimen due to treatment failure, with a median treatment duration of 1.2 years. In comparison, the cumulative incidence of treatment failure in a cohort of 1370 adult patients in a study from the largest public HIV care centre in India was 3.9% (95% CI 2.9 to 4.9) [10].

A good proportion of cases of treatment failure in our study (30.9%) were detected early by means of quantitative PCRs for Viral RNA, which is offered to all patients who can afford the viral load testing, in our centre. There is evidence that in resource-limited settings as well, CD4 count and HIV RNA monitoring to guide switching to second-line ART improves survival and, under most conditions, is cost effective. About three-quarters of our cases i.e., 78.5% of the cases were diagnosed as treatment failure based on a quantitative HIV RNA PCR and a significant number of these (21/33) also had genotypic resistance testing done. All the patients in whom genetic resistance testing was done, there was high-level resistance to NNRTIs (NVP/EFV) and NRTIs (3TC/FTC). The most common mutations found were Y181C, K103N & M184I/V, D67N, K70E, V75M and M41L. These findings are consistent with the findings from other studies in India and other developing countries [45-46]. A study

from Southern India which included 138 patients with treatment failure on generic first-line ART found, that of the NRTI resistance mutations, M184V was the most common (79%). Thymidine analogue mutations (TAMS) including M41L, T215Y/F, L210W, D67N, K219E/Q and K70R were found in 60% of patients. In the same study, NNRTI resistance mutations were in 88% of the patients and included K103N, Y181C, and G190A[47]. However, drug resistance patterns in developed countries differ from that seen in our study, largely due to the difference in profile of first-line ART regimens being used (NNRTI-based Vs. PI-based[48].

Three variables were found to be significantly associated with treatment failure(after a logistic regression analysis) in our study, namely, *Non-adherence as reported by the patients themselves, history of prolonged diarrhoea* and *drug toxicity to any antiretroviral drug or Cotrimoxazole.*

Poor adherence was an important risk factor for treatment failure on ART [OR = *15.46]*. A retrospective longitudinal analysis of HIV-infected patients followed in the Massachusetts General Hospital found poor adherence as a risk factor for treatment failure with HR of 3.44(95%CI:2.34 to 5.05). The degree of difference could possibly be explained by the fact that NNRTI based regimens tend to be unforgiving, as resistance develops sooner, and also that the levels of health literacy differ in developed and developing nations[32]. Our study provides further confirmation of *adherence* as an important determinant of subsequent treatment failure, and serves as a reminder of the importance of initial early investments in adherence counselling and support. This is probably the most effective way to maximize long-term treatment success in this population. The importance of adherence in the success of antiretroviral therapy has been

shown repeatedly in various studies. [11-15][5], even though the strength of this relationship may vary with different population sub-groups.

Interruptions in treatment schedules (as brief as 10days to as long as 6months), in otherwise adherent patients may also be associated with treatment failure. In our study, treatment interruptions were largely unstructured. It was either physician advised (in view of serious drug toxicity) or due to patient-related problems (various social issues – intercurrent illness/presumed toxicity/inability to procure medications etc,.).

Past inappropriate therapy (inappropriate schedule/inadequate drug dosing) is also a recognised risk factor for failure of anti-retroviral therapy, due to sub-optimal therapeutic levels to suppress viral replication resulting in emergence of resistance. Our study had a significant number of patients with a past history of initial dual therapy (16.6%) all started elsewhere, possibly due to lack of knowledge among the HIV care physicians or inaccessibility of specialist care. There is strong evidence that management of complex HIV and HAART related issues by a specialist physician leads to better patient outcomes [49-51]. The greater cost and lack of knowledge regarding the anti-retroviral drugs prior to advent of the NACO-ART programme may also have contributed to initiation of inappropriate therapies by the General practitioners.

There has been a growing concern over the possibility that many patients globally are experiencing virological failure despite high levels of adherence to generic NNRTI-based HAART, a frequently used first line therapy in global antiretroviral (ARV) scale-up efforts. This seeming discordance in adherence and virological response has prompted search for other possible risk factors. Chronic diarrhoea is one of the most common

symptoms of HIV/AIDS in resource-limited countries. It results in decreased quality of life, progressive wasting and nutrient deficiencies. It is also associated with increased early mortality in patients presenting for ART [52]. There is evidence that antiretroviral drugs are poorly absorbed in most patients with diarrhoea and wasting, and this may lead on to drug resistance, due to presence of sub-therapeutic serum drug levels for prolonged periods of time [41][53]. Altered gut motility (possibly due to increased parasympathetic drive) and defective absorption may also play a role in AIDS-related pathogen-negative diarrhoeas [53-54]. In our study, history of prolonged diarrhoea (documented in the chart) was identified as a risk factor for treatment failure [*OR of 23.446]*. In a developing nation, lack of proper food hygiene combined with poor sanitation and cultural practices may predispose immune-compromised individuals to frequent diarrhoeal illnesses and there-by contribute further to malnutrition and eventual poor outcomes. At present, there is a no clear data implicating diarrhoea as a predictor of treatment failure. The findings of this study should prompt further research into measuring the impact of diarrhoea on drug resistance and treatment failure.

Presence of other medical co-morbidities such as diabetes, hypertension, dyslipidemia, ischemic heart disease and renal failure results in patients having to take multiple drugs and a high pill burden (also, considered to be a surrogate for treatment regimen complexity) has been found to be consistently associated with a higher likelihood of discontinuation of antiretroviral therapy[55]. Other co-morbidities such as alcoholism may also contribute towards patients being non-adherent to therapy [56].

In a cohort of HIV-infected patients from the USA including 3414 ART-naïve patients on HAART with a median follow-up period of 211 days; the main causes for discontinuation of therapy were drug toxicity (18.4%), non-compliance(13.4%), and

treatment failure(7.5%)[56]. Patients vary in their ability to tolerate side effects. A bad physician-patient rapport will lead to reluctance on the part of the patient to report minor adverse drug effects and thus contribute to poor adherence and subsequently treatment failure.

There is a large inter-individual variability in plasma drug levels achieved in patients on antiretroviral therapy. Recent pharmacogenetic studies of antiretroviral drugs in humans have reported that several genetic polymorphisms may have a significant influence on antiretroviral drug exposure, toxicity and response to treatment[57]. This may be another mechanism that could link drug toxicity with treatment failure, other than the well known theory of non-adherence/interruption of therapy.

# CONCLUSIONS

- NNRTI resistance with Y181C & K103N mutations and Lamivudine resistance with M181V mutation and other TAMs was common (21/21=100%) in this group of patients with treatment failure.
- There is a strong association of treatment failure on anti-retroviral therapy with simple clinical parameters – Self reported non-adherence, history of prolonged diarrhoea and presence of any adverse drug effect.
- Adherence >95% is an important determinant for success of antiretroviral therapy, Hence stringent adherence counselling is imperative prior to initiation of HAART and reinforcement at each subsequent visit is likely to improve treatment outcomes.
- In a patient with history of prolonged diarrhoea, malabsorption should be looked for and ruled out, to ensure adequate therapeutic drug levels. Therapeutic drug monitoring when available could be used in such situations.
- Early detection of drug toxicities and prompt management of the same could prevent clinically significant interruptions of therapy.

# LIMITATIONS

1. Small sample size
2. Wide confidence intervals may require cautious interpretation of the strength of association
3. A sizeable amount of missing data in the out-patient and in-patient charts of the cohort.

# BIBLIOGRAPHY:


1. Steinbrook, R., *HIV in India -- A Complex Epidemic.* N Engl J Med, 2007. **356**(11): p. 1089-1093.
2. Rewari, B.B. and S. Tanwar, *Emergencies in HIV medicine.* J Indian Med Assoc, 2009. **107**(5): p. 317-22.
3. WORLD HEALTH ORGANISATION and UNAIDS, *AIDS epidemic update*
4. George, C., et al., *A prospective study evaluating clinical outcomes and costs of three NNRTI-based HAART regimens in Kerala, India.* J Clin Pharm Ther, 2009. **34**(1): p. 33-40.
5. Bangsberg, D.R., et al., *Provider assessment of adherence to HIV antiretroviral therapy.* J Acquir Immune Defic Syndr, 2001. **26**(5): p. 435-42.
6. Colebunders, R., et al., *A new model to monitor the virological efficacy of antiretroviral treatment in resource-poor countries.* Lancet Infect Dis, 2006. **6**(1): p. 53-9.
7. Wainberg, M.A. and G. Friedland, *Public health implications of antiretroviral therapy and HIV drug resistance.* JAMA, 1998. **279**(24): p. 1977-83.
8. Weidle, P.J., et al., *Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance.* Lancet, 2002. **360**(9326): p. 34-40.
9. Dragsted, U.B., et al., *Predictors of immunological failure after initial response to highly active antiretroviral therapy in HIV-1-infected adults: a EuroSIDA study.* J Infect Dis, 2004. **190**(1): p. 148-55.
10. Rajasekaran, S., et al., *Predictors of failure of first-line antiretroviral therapy in HIV-infected adults: Indian experience.* AIDS, 2007. **21 Suppl 4**: p. S47-53.
11. Gross, R., et al., *Effect of adherence to newly initiated antiretroviral therapy on plasma viral load.* AIDS, 2001. **15**(16): p. 2109-17.
12. Gifford, A.L., et al., *Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens.* J Acquir Immune Defic Syndr, 2000. **23**(5): p. 386-95.

13. Paterson, D.L., et al., *Adherence to protease inhibitor therapy and outcomes in patients with HIV infection.* Ann Intern Med, 2000. **133**(1): p. 21-30.
14. Haubrich, R.H., et al., *The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group.* AIDS, 1999. **13**(9): p. 1099-107.
15. Casado, J.L., et al., *Predictors of long-term response to protease inhibitor therapy in a cohort of HIV-infected patients.* AIDS, 1998. **12**(11): p. F131-5.
16. Hogg, R.S., et al., *Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up.* AIDS, 2002. **16**(7): p. 1051-8.
17. Bangsberg, D.R., et al., *Non-adherence to highly active antiretroviral therapy predicts progression to AIDS.* AIDS, 2001. **15**(9): p. 1181-3.
18. Garcia de Olalla, P., et al., *Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients.* J Acquir Immune Defic Syndr, 2002. **30**(1): p. 105-10.
19. Low-Beer, S., et al., *Adherence to triple therapy and viral load response.* J Acquir Immune Defic Syndr, 2000. **23**(4): p. 360-1.
20. Golin, C.E., et al., *A prospective study of predictors of adherence to combination antiretroviral medication.* J Gen Intern Med, 2002. **17**(10): p. 756-65.
21. Miller, L.G., et al., *Knowledge of antiretroviral regimen dosing and adherence: a longitudinal study.* Clin Infect Dis, 2003. **36**(4): p. 514-8.
22. Mannheimer, S., et al., *The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials.* Clin Infect Dis, 2002. **34**(8): p. 1115-21.
23. Bangsberg, D.R., et al., *Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population.* AIDS, 2000. **14**(4): p. 357-66.
24. Wagner, G.J., et al., *Adherence to HIV antiretrovirals among persons with serious mental illness.* AIDS Patient Care STDS, 2003. **17**(4): p. 179-86.
25. Howard, A.A., et al., *A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women.* AIDS, 2002. **16**(16): p. 2175-82.
26. McNabb, J., et al., *Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic.* Clin Infect Dis, 2001. **33**(5): p. 700-5.

27. Arnsten, J.H., et al., *Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring.* Clin Infect Dis, 2001. **33**(8): p. 1417-23.
28. Ickovics, J.R., et al., *Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370.* Antivir Ther, 2002. **7**(3): p. 185-93.
29. Ickovics, J.R. and C.S. Meade, *Adherence to antiretroviral therapy among patients with HIV: a critical link between behavioral and biomedical sciences.* J Acquir Immune Defic Syndr, 2002. **31 Suppl 3**: p. S98-102.
30. Gordillo, V., et al., *Sociodemographic and psychological variables influencing adherence to antiretroviral therapy.* AIDS, 1999. **13**(13): p. 1763-9.
31. Kleeberger, C.A., et al., *Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the Multicenter AIDS Cohort Study.* J Acquir Immune Defic Syndr, 2001. **26**(1): p. 82-92.
32. Kalichman, S.C., B. Ramachandran, and S. Catz, *Adherence to combination antiretroviral therapies in HIV patients of low health literacy.* J Gen Intern Med, 1999. **14**(5): p. 267-73.
33. Chesney, M.A., *Factors affecting adherence to antiretroviral therapy.* Clin Infect Dis, 2000. **30 Suppl 2**: p. S171-6.
34. Wagner, G.J., *Predictors of antiretroviral adherence as measured by self-report, electronic monitoring, and medication diaries.* AIDS Patient Care STDS, 2002. **16**(12): p. 599-608.
35. (WHO), W.H.O., *Antiretroviral therapy for HIV infection in adults.* november 2009.
36. Mocroft, A., et al., *Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor.* AIDS, 1998. **12**(16): p. 2161-7.
37. Lucas, G.M., R.E. Chaisson, and R.D. Moore, *Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions.* Ann Intern Med, 1999. **131**(2): p. 81-7.
38. Deeks, S.G., et al., *HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy.* AIDS, 1999. **13**(6): p. F35-43.

39. Boffito, M., et al., *Current status and future prospects of therapeutic drug monitoring and applied clinical pharmacology in antiretroviral therapy.* Antivir Ther, 2005. **10**(3): p. 375-92.
40. Piscitelli, S.C. and K.D. Gallicano, *Interactions among drugs for HIV and opportunistic infections.* N Engl J Med, 2001. **344**(13): p. 984-96.
41. Bushen, O.Y., et al., *Diarrhea and reduced levels of antiretroviral drugs: improvement with glutamine or alanyl-glutamine in a randomized controlled trial in northeast Brazil.* Clin Infect Dis, 2004. **38**(12): p. 1764-70.
42. Daniel González de Requena, I.J.-N., and Vincent Soriano, *Therapeutic Drug Monitoring for Antiretroviral Therapy: Usefulness and Limitations.* AIDS reviews, 2000. **2**: p. 67-75.
43. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf. 2006.
44. Shah, B., et al., *Adherence to antiretroviral therapy and virologic suppression among HIV-infected persons receiving care in private clinics in Mumbai, India.* Clin Infect Dis, 2007. **44**(9): p. 1235-44.
45. *Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa.* AIDS, 2006. **20**(10): p. 1391-9.
46. Marconi, V.C., et al., *Prevalence of HIV-1 drug resistance after failure of a first highly active antiretroviral therapy regimen in KwaZulu Natal, South Africa.* Clin Infect Dis, 2008. **46**(10): p. 1589-97.
47. Kumarasamy, N., et al., *High frequency of clinically significant mutations after first-line generic highly active antiretroviral therapy failure: implications for second-line options in resource-limited settings.* Clin Infect Dis, 2009. **49**(2): p. 306-9.
48. http://hivdb.stanford.edu/cgi-bin/Summary.cgi.
49. Stone, V.E., et al., *The relation between hospital experience and mortality for patients with AIDS.* JAMA, 1992. **268**(19): p. 2655-61.
50. Kitahata, M.M., et al., *Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival.* N Engl J Med, 1996. **334**(11): p. 701-6.
51. Palella, F.J., Jr., et al., *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.* N Engl J Med, 1998. **338**(13): p. 853-60.

52. Dillingham, R.A., et al., *High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study.* Am J Trop Med Hyg, 2009. **80**(6): p. 1060-4.
53. Lambl, B.B., et al., *Malabsorption and wasting in AIDS patients with microsporidia and pathogen-negative diarrhea.* AIDS, 1996. **10**(7): p. 739-44.
54. Coker, R.J., et al., *Increased gut parasympathetic activity and chronic diarrhoea in a patient with the acquired immunodeficiency syndrome.* Clin Auton Res, 1992. **2**(5): p. 295-8.
55. Yuan, Y., et al., *Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort.* HIV Med, 2006. **7**(3): p. 156-62.
56. Samet, J.H., et al., *Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems.* Alcohol Clin Exp Res, 2004. **28**(4): p. 572-7.
57. Cressey, T.R. and M. Lallemant, *Pharmacogenetics of antiretroviral drugs for the treatment of HIV-infected patients: an update.* Infect Genet Evol, 2007. **7**(2): p. 333-42.

# ANNEXURE:

Proforma

**A CASE-CONTROL STUDY ON PREDICTORS OF TREATMENT FAILURE IN PEOPLE LIVING WITH HIV/AIDS(PLWHA) ON ART IN A HIV CLINIC FROM SOUTH INDIA**

Proforma No:

Name:

Hospital No:

Sex: Male / Female

Age in years: yrs

Demographics:

BMI:

**Ht(cm) & Wt.(Kg)**

**Kuppuswamy's Socioeconomic Status Scale**

| **(A) Education** | **Score** |
|---|---|
| 1. Profession or Honours | 7 |
| 2. Graduate or post graduate | 6 |
| 3. Intermediate or post high school diploma | 5 |
| 4. High school certificate | 4 |
| 5. Middle school certificate | 3 |
| 6. Primary school certificate | 2 |
| 7. Illiterate | 1 |

| **(B) Occupation** | **Score** |
|---|---|
| 1. Profession | 10 |
| 2. Semi-Profession | 6 |
| 3. Clerical, Shop-owner, Farmer | 5 |

| | | | |
|---|---|---|---|
| 4. Skilled worker | | 4 | |
| 5. Semi-skilled worker | | 3 | |
| 6. Unskilled worker | | 2 | |
| 7. Unemployed | | 1 | |
| **(C) Family income per month(in Rs)- original** | **Score** | **Modified for 1998** | **Modified for 2007** |
| 1. =2000 | 12 | =13500 | =19575 |
| 2. 1000-1999 | 10 | 6750-13499 | 9788-19574 |
| 3. 750-999 | 6 | 5050-6749 | 7323- 9787 |
| 4. 500-749 | 4 | 3375-5049 | 4894- 7322 |
| 5. 300-499 | 3 | 2025-3374 | 2936-4893 |
| 6. 101-299 | 2 | 676-2024 | 980-2935 |
| 7. =100 | 1 | =675 | =979 |

| **Total Score** | **Socioeconomic class** |
|---|---|
| 26-29 | Upper (I) |
| 16-25 | Upper Middle (II) |
| 11-15 | Middle Lower middle (III) |
| 5-10 | Lower Upper lower (IV) |
| <5 | Lower (V) |

Date of diagnosis of HIV infection: (DD/MM/YYYY)

Risk Factor: Heterosexual / Homosexual / MSM / Blood Transfusion / Needle stick injury /MTCT

Risk Factor Others:

Type of test for HIV: ELISA / Western blot / Rapid

VDRL: Reactive / Non Reactive / Not done

HBsAg : Reactive / Non Reactive / Not done

HCV infection: Reactive/ Non-reactive/ Not done

**OI before ART**

| Date | OI | Proven | Presumed |
|---|---|---|---|
| | TB Pulmonary<br>TB Disseminated<br>Bacterial Pneumonia | | |
| | **TB extrapulmonary** | | |
| | **Candidiasis**<br>1.Oral<br>2. Oesophageal | | |
| | Cryptococcosis | | |
| | PCP | | |
| | Cerebral Toxoplasmosis | | |
| | **Chronic diarrhea (pathogen)**<br>1. Isospora<br>2. Cyclospora<br>3. Microsporidium<br>4. Cryptosporidium<br>5. Giardia<br>6. Others | | |
| | Bacterial infections (specify) | | |
| | **CMV**<br>1. Eye<br>2. GI<br>3. CNS<br>4. Disseminated | | |
| | **Neurological Diseases**<br>1. Dementia<br>2. Peripheral Neuropathy<br>3. Transverse Myelitis<br>4. GBS | | |

| | | | |
|---|---|---|---|
| | 5. CIDP<br>6. Others | | |
| | **STI**<br>1. Syphilis<br>2. Herpes Genitalis<br>3. Herpes Zoster<br>4. Herpes Symplex<br>5. Gonorrhea | | |
| | PMLE | | |
| | Others (specify) | | |

Baseline Investigations (within 30 days before starting ART)

Hb : TC : DC:

Platelets:

S. Creatinine

LFT

Lipids

Chest Xray

WHO Stage: 1 / 2 / 3 / 4 prior to ART

Other diseases prior to ART

Date

i) **Measure of Adherence: >95% or 80-95% or <80%**

Self-reported -

Pill count/Pill-boxes –

Pill Burden -

ii) **Markers for possible malabsorption:**

Documented gastro-intestinal OI

Diarrhea ( Stool frequency )

Albumin (Baseline)

Change in Albumin (since HAART)

Weight gain since initiation of ART

iii) **Medical co-morbidities:**

Diabetes mellitus

Hypertension

Dyslipidemia

Alcoholism

Renal failure

Others

iv) **Type of treatment failure :**

Clinical progression/rebound

Immunological failure

Virological failure

**v) Other drugs with possible interactions:**
**List**

**Initial HAART: WHO – NACO free generic ART/ payment**

**Regimen:**

**Date started:** **stopped / switched/substituted**

**Duration of initial regimen (months):**

**If stopped, reason for stopping HAART:**

1. Virologic failure
2. Immunologic failure
3. Clinical failure
4. Drug toxicity
5. Co-morbidities
6. IRIS
7. Drug intolerance

**DRUG TOXICITY** **Onset of toxicity after HAART (days)**

1. Rash Date
2. Lactic acidosis Date
3. Hepatitis Date
4. Anemia Date
5. Leukopenia Date
6. Thrombocytopenia Date
7. Peripheral neuropathy Date
8. Glucose intolerance/ diabetes Date

9. Dyslipidemia Date
10. Lipodystrophy Date
11. Pancreatitis Date
12. Renal failure Date
13. Others

IRIS: Yes /No

How long after start of HAART

What IRIS

Treatment given: Conservative / pathogen specific / steroids/ vitamins

HAART stopped/ modified

**HAART regimen 2:** **Date start:** **Date stop:**

**Reason .....**

**HAART regimen 3:** **Date start:** **Date stop:**

**Follow-up**

| Visit Date (DD/MM/YYYY) | Weight (Kgs) | Adherence (%) | Toxicity | CD4 Cells (/µl) | Viral load (RNA Copies/ml) | IRIS | New events |
|---|---|---|---|---|---|---|---|
| Baseline | | | | | | | |
| 6 months | | | | | | | |
| 12 months | | | | | | | |
| 18 months | | | | | | | |
| 24 months | | | | | | | |
| 36 months | | | | | | | |
| 48 months | | | | | | | |
| 60 months | | | | | | | |

Current status : Alive / Dead

## ***Data sheets:***